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| 10/606,320      | 06/25/2003  | Andre R. Abad        | 035718/263948       | 8411             |

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ALSTON & BIRD LLP  
PIONEER HI-BRED INTERNATIONAL, INC.  
BANK OF AMERICA PLAZA  
101 SOUTH TYRON STREET, SUITE 4000  
CHARLOTTE, NC 28280-4000

EXAMINER

MAYER, SUZANNE MARIE

ART UNIT PAPER NUMBER

1653

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/606,320

Applicant(s)

ABAD ET AL.

Examiner

Suzanne M. Mayer, Ph.D.

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 03 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) 7-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 June 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 8/14/03, 1/08/04, 4/2/04, 11/5/04
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election with traverse of Group I, claims 1-9 in the reply filed on December 03, 2004 is acknowledged. The traversal is on the grounds that Group II, claims 10-19, is inconsistent with the restriction pattern of the rest of the office action and that this group should have been further restricted into two groups, that being claims 10-13 and claims 14-19. This is not found persuasive because the claims are drawn to the same scope of invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7-56 have been cancelled by Applicant, thus the pending claims in the present application are claims 1-6.

### ***Information Disclosure Statement***

2. The information disclosure statements (IDS) submitted on August 14, 2003; January 8, 2004; April 2, 2004 and November 5, 2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner. See attached and signed PTOL-1449's.

### ***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1 and 4-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. Chen et al. teach the engineering of proteolytic cathepsin sites for the delta-endotoxin Cry3A from *Bacillus thuringiensis*. The introduction of these manufactured proteolytic sites shows significant increases in the pesticidal activity of the delta-endotoxins as compared to the wild-type endotoxin (see paragraph [0018] and Example 4). The engineered cathepsin proteolytic sites are introduced into domain I and/or domain III of Cry3A of SEQ ID No: 2 and/or 4 (SEQ ID No: 4 is a shorter version of SEQ ID No: 2, which is missing a naturally occurring cleavage site on one of the terminus'). In domain I, an engineered cathepsin proteolytic site is introduced between residues 154-158 (see paragraphs [0023 and 0122]) for SEQ ID No: 2. According to the three-dimensional protein crystal structure of Cry3A from Li et al., which is the same protein as SEQ ID No: 2 of Chen et al., these residues are located on a loop between alpha helices 3 and 4 in domain I (see Li et al., cited on PTOL-1449 of 8/14/2003, p. 819, Figure 3). Introduction of cathepsin proteolytic sites in domain III is also taught, and is performed either singly or in addition to the introduced site in domain I, so that there are two engineered sites in Cry3A. The alteration in domain III occurs with the introduction of a cathepsin proteolytic site which is inserted between residues 587 and 588 for SEQ ID No: 2 (see paragraphs [0029 and 0127]).

Specific sequences with modified and introduced cathepsin proteolytic sites are taught in such as SEQ ID No: 16 which is a 1812-1 modified endotoxins. This specific endotoxin has been modified from SEQ ID No: 4 by the introduction of engineered cathepsin proteolytic sites inserted between residues 107 and 113 of domain I of SEQ ID No: 4 (which is located on the loop between alpha-helices 3 and 4) and residues 536 and 541 of domain III. The 1812-1 endotoxins are described in the specification of the instant application.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. and further in view of Audtho et al.

The teachings of Chen et al. are described above. However, Chen et al. do not teach the introduction of additional mutations to naturally occurring proteolytic sites that also enhance the stability of the endotoxin.

Audtho et al. teaches the introduction of a single point mutation at a natural proteolytic cleavage site in domain I of the endotoxin Cry2Aa1. The mutation at residue Leucine 144 by aspartate, alanine, glycine, histidine and valine confer increased stability of the endotoxin as it is more resistant to protease degradation than the wild-

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type endotoxin (see p. 4603, 1<sup>st</sup> column, 2<sup>nd</sup> and 3<sup>rd</sup> paragraphs). While it was noted that the stability increased in the endotoxin compared to the wild-type toxin, the toxicity levels remained the same (see p. 4604, 2<sup>nd</sup> column, 2<sup>nd</sup> to last paragraph, lines 7-9).

One of ordinary skill in the art would be motivated to combine the teachings of Chen et al. with that of Adutho et al. because it would be highly desirable to have an endotoxin which conferred BOTH higher toxicity AND stability.

Chen et al. teach the methods and identify sequences which have engineered cathepsin sites in domain I and/or domain III of an endotoxin. The introduction of one or both of these sites into the wild-type toxin increases the toxicity of the endotoxin. While Adutho et al. does not teach increased toxicity in an endotoxin, they do teach how to engineer an endotoxin that is more stable than the wild-type toxin by replacing a leucine which is at the site of a naturally occurring proteolytic site, with among other amino acids, a valine residue.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Adutho et al. in order to increase the stability of an endotoxin with the teachings of Chen et al. in order to create an endotoxin which is both more toxic and stable than the wild-type toxin.

### ***Conclusion***

7. No claim is allowed.
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Mayer, Ph.D. whose telephone number is

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571-272-2924. The examiner can normally be reached Monday to Friday, 8.30am to 5.00pm.

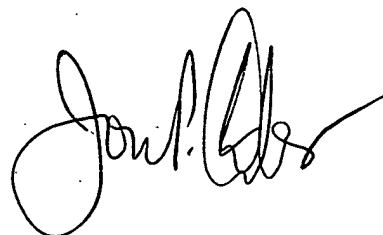
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



SMM

21 January, 2005



**JON WEBER**  
**SUPERVISORY PATENT EXAMINER**